सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.**1097/Del/02** dated **31st October 2002.***

Witness my hand this 16th day of January 2004.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

(S.K. PANGASA)
Assistant Controller of Patents & Designs

FORM 1 1097 DEL 02

THE PATENTS ACT, 1970
(39 of 1970)

31 OCT 2002

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"COMMERCIAL PROCESS FOR THE PREPARATION OF N^2-ACETYL-9-(1,3-DIACETOXY-2-PROPOXYMETHYL) GUANINE"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. JAYACHANDRA SURESH BABU
b. PURNA CHANDRA RAY
c. CHANDRA HAS KHANDURI
d. YATENDRA KUMAR

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10
Fax No. (91-124) 6342027

DUPLICATE

6. Following declarat[redacted] was given by the inventors in the conve[redacted] country:

We, JAYACHANDRA SURESH BABU, PURNA CHANDRA RAY, CHANDRA HAS KHANDURI, YATENDRA KUMAR, of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (JAYACHANDRA SURESH BABU)

b. (PURNA CHANDRA RAY)

c. (CHANDRA HAS KHANDURI)

d. (YATENDRA KUMAR)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **685261** dated **22.10.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **28TH** day of **October, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

10 DEL 02

31 OCT 2002

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

DUPLICATE

COMMERCIAL PROCESS FOR THE PREPARATION OF N^2-ACETYL-9-(1,3-DIACETOXY-2-PROPOXYMETHYL) GUANINE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a commercial process for the preparation of N^2-Acetyl-9-(1,3-diacetoxy-2-propoxymethyl) guanine referred to here as N-alkylated isomer of structural formula I as shown in the accompanied drawings , useful as an intermediate for the preparation of antiviral compound, ganciclovir.

Ganciclovir was disclosed in the US Patent No.4,355,032 by Syntex. It is chemically known as 9-(1,3-dihydroxy-2-propoxymethyl)guanine and has the structural formula II as shown in the accompanied drawings, is one of the most important acyclic nucleosides having significant antiviral properties. It is highly efficacious against members of the herpes family and cytomegalovirus.

Similarly a number of other associated prodrugs and other purine derivatives have been reported as pharmacologically important. Acyclovir is administered therapeutically for the treatment of herpes simplex virus.

The strategy adopted in prior art for the manufacture of these purine nucleosides comprises of treating appropriately substituted 2-aminopurines e.g. guanine derivatives with required addendum to provide the alkylated intermediate which on deprotection of the functional group are converted to final product .

During the course of the present investigation, it has been discovered that diacetyl guanine (DAG) the starting material for preparing ganciclovir may be converted to monoacetyl guanine (MAG) , some of which remains unreacted during the condensation.

There are significant drawbacks to these approaches as the penultimate intermediate i.e. condensed product always results with:

(a) unreacted starting material i.e. diacetyl or monoacetyl guanine of structural formula III and IV respectively as shown in the accompanied drawings.

(b) N^2-Acetyl-7-(1,3-diacetoxy-2-propoxymethyl) guanine, referred to as N-7 isomer of structural formula V as shown in the accompanied drawings.

(c) polar impurities

The prior art approach was not suitable from commercial point of view because the desired N-9 isomer required purification by tedious and cumbersome purification processes such as column chromatography , HPLC or other conventional techniques, usage of expensive chemical solvents making the approach commercially difficult to implement.

The above methods has drawbacks in that the desired products are not obtained in high yields and high purity which results in the formation of ganciclovir in less yield and thus making the process complicated from the industrial point of view. Shortcomings in any of the parameters result in increased manufacturing cost which impacts negatively on the desirability of the process.

To achieve a high efficiency of reaction for industrial scale synthesis of ganciclovir, it is necessary to minimize the unreacted diacetyl or monoacetyl guanine , N-7 isomer and polar impurities.

Thus the present invention provides a process which does not require the purification of intermediate by HPLC or other conventional techniques, rather uses organic solvents and / or water or mixtures thereof . The choice of which has been found to be important for removing the traces of polar and non- polar impurities.

Accordingly, the present invention provides an efficient process to overcome the problems associated with the prior art and improves the economics by resulting in higher yields of the desired isomer and less reaction time.

The process of the present invention reduces the impurity of the penultimate intermediate of ganciclovir, eliminates the costly and time consuming purification steps which in turn improves

the economics by resulting in higher yields of the desired isomer and less reaction time. The process is industrially useful and also easy to handle and avoids chromatographic separation of the N-9 and N-7 isomers and the increased cost associated with such a separation.

The present inventors have conducted extensive studies. As a result they have developed a commercial process to prepare ganciclovir in better yields by purifying the intermediate N-9 isomer, as the quality of finished product is dependent on the quality of the intermediates.

The above objects and advantages have been achieved by a process for producing ganciclovir in better quality by selectively removing the polar and non polar impurities present in N-9 isomer. The purified intermediate thus obtained is directly deprotected to remove the esters and converted to product.

Ganciclovir is prepared by condensing protected guanine derivative with the side chain. The condensed product N-9 isomer. thus formed is deprotected and converted to ganciclovir..

In accordance with the present invention, the process of purifying N-9 isomer, comprises treating N-9 isomer with organic solvents, water or mixtures thereof. The said organic solvents comprises lower alkanols, acetone and water-immiscible solvents and mixtures thereof.

The lower alkanols comprises primary, secondary and tertiary alcohols having one to six carbon atoms preferably selected from primary, secondary and tertiary alcohols having one to four carbon atoms such as methanol, ethanol, n-propyl alcohol, iso propyl alcohol, isobutanol, n-butanol, t-butanol or mixtures thereof.

Water-immiscible solvents are selected from the group comprising aromatic hydrocarbons and chlorinated hydrocarbons.

The said chlorinated hydrocarbons comprise at least one of chloroform, dichloromethane, and 1,2-dichloroethane.

A preferred embodiment of this aspect of the present invention comprises dissolving N-9 isomer in a mixture of organic solvents upon heating. The organic solvents used above are selected from ethanol, methanol, dichloromethane, dichloroethane, or mixtures thereof.

A further aspect of the present invention is filtering the unreacted solid , removing the solvent to obtain a residue and then adding organic solvents preferably a polar solvent, such as acetone to give a better yield of N-9 isomer.

The results mentioned in the tables given in examples clearly illustrate that the better yield of N-9 isomer is obtained on purification.

Methods known in the art may be used with the process of this invention to enhance any aspect of this invention. For example, the solution containing the mixture of N-7 and N-9 isomers may be heated for dissolution, or may be cooled to separate out the product or the slurry may further be cooled prior to filtration.

The N-9 isomer so obtained after separation is hydrolyzed to yield ganciclovir by the methods known in the literature (J.E. Martin et. al. J. Med. Chem., 1983,26, 759-761).

Other features of the invention will become apparent in the course of the following description of exemplary embodiment which is given for illustration of the invention and are not intended to be limited thereof.

To further illustrate the present invention and not by way of limitation, the following examples are given:

EXAMPLE 1

Crude N^2-Acetyl-9-(1,3-diacetoxy-2-propoxymethyl)guanine (100 kg) was added to the mixture of dichloromethane (500 lit.) and methanol (40 lit.). Temperature was raised to 30-35°C and maintained for 30 minutes. and then activated carbon (5 kg) was added and stirred for another 30 minutes at the same temperature. Slowly cooled to 5°C and maintained for 30 minutes. Filtered through hyflo bed, removed the solvent completely by distillation, added acetone (800 lit.) to the resulting mass. Cooled to 35°C, stirred for 60 minutes. at 30-35°C. Filtered the solids and washed with acetone, yielding 80 - 82 kg of pure N^2-Acetyl -9-(1,3-diacetoxy-2-propoxymethyl) guanine.

Data on chromatographic purity	**Before Purification**	**After Purification**
N-9 isomer	95.08	98.90
DAG / MAG	2.77	0.1
N-7 isomer	0.62	0.11

EXAMPLE 2

Crude N^2-Acetyl -9-(1,3-diacetoxy-2-propoxymethyl) guanine (100 gm) was added to the mixture of dichloromethane (500 ml) and methanol (40 ml). Temperature was raised to 30-35°C and kept for 30 minutes, and then activated carbon (5 gm) was added and stirred for another 30 minutes at the same temperature. Slowly cooled to 8°C and maintained for 30 minutes. Filtered through hyflo bed, washed the bed using dichloromethane. Distilled off the solvents completely under vacuum. Charged fresh dichloromethane (200 ml) and heated up to 40°C followed by cooling to 2-5°C. Filtered the product and washed with dichloromethane. Collected the wet material and charged acetone (700 ml) to the wet mass and heated to reflux temperature. Cooled to 35°C stirred 60 minutes at 30-35°C. Filtered the solids and washed with acetone, yielding 68-72 gm of pure N^2-Acetyl -9-(1,3-diacetoxy-2-propoxymethyl) guanine after drying.

Data on chromatographic purity	Before Purification	After Purification
N-9 isomer	88.73	98.63
DAG / MAG	7.9	0.31
N-7 isomer	1.08	0.25

EXAMPLE 3

Crude N^2-Acetyl -9-(1,3-diacetoxy-2-propoxymethyl)guanine (100 gm) was added to the DM water (250 ml.) at room temperature. Temperature was raised to 70 - 75°C and kept 30 minutes, all solids completely dissolved at the same temperature. Slowly cooled to room temperature followed by further cooling to 5-10°C and maintained for 60 minutes. Filtered the product at 5°C, yielding 58 gm of pure N^2-Acetyl -9-(1,3-diacetoxy-2-propoxymethyl)guanine after drying.

Data on chromatographic purity	Before Purification	After Purification
N-9 isomer	77.15	86.73
DAG / MAG	3.01	1.65
N-7 isomer	13.64	6.64

EXAMPLE-4

Crude N^2-Acetyl -9-(1,3-diacetoxy-2-propoxymethyl)guanine (400 gm) was added to methanol (1.25 lit.) at room temperature. Temperature was raised to 40 - 45°C and kept for 30 minutes, all solids completely dissolved at the same temperature. Slowly cooled to room temperature followed by further cooling to 5°C and maintained for 60 minutes. Filtered the product at 5°C and washed using chilled methanol, yielding 220 gm of pure N^2-Acetyl -9-(1,3-diacetoxy-2-propoxymethyl)guanine after drying.

Data on chromatographic purity	**Before Purification**	**After Purification**
N-9 isomer	88.41	94.09
DAG / MAG	1.71	0.34
N-7 isomer	4.83	1.06

WE CLAIM:

1. A process for the purification of N^2-Acetyl-9- (1,3-diacetoxy-2-propoxymethyl)guanine of structural formula I as shown in the accompanied drawings comprising the step of treating crude N^2-Acetyl-9-(1,3-diacetoxy-2-propoxymethyl) guanine with organic solvents, water or mixtures thereof.

2. The process of claim 1 wherein organic solvent comprises lower alkanols, acetone, water-immiscible solvents and mixtures thereof.

3. The process of claim 2 wherein lower alkanol comprises primary, secondary and tertiary alcohols having 1 to 6 carbon atoms.

4. The process of claim 2 wherein lower alkanol comprises primary, secondary and tertiary alcohols having 1 to 4 carbon atoms.

5. The process of claim 4 wherein lower alkanol is selected from methanol, ethanol, n-propyl alcohol, iso- propyl alcohol, iso-butanol, n-butanol, t-butanol , or mixtures thereof.

6. The process of claim 2 wherein the water-immiscible solvent is selected from the group comprising aromatic hydrocarbons and chlorinated hydrocarbons.

7. The process of claim 6 wherein said chlorinated hydrocarbon comprises at least one of chloroform , dichloromethane and 1,2- dichloroethane.

8. The process of claim 1, comprises dissolving said N-9 isomer in crude form in the organic solvent, water or mixtures thereof by heating, followed by cooling and filtering the unreacted solid to obtain a residue.

9. The process of claim 8 further comprises treating the obtained residue optionally with a polar solvent.

10. A process for the hydrolysis of N-9 isomer of structural formula I as shown in the accompanied drawings prepared by the process of claim 1 to give ganciclovir of structural formula II.

11. A process for the preparation of N-9 isomer of structural formula I as shown in the accompanied drawings substantially described herein and exemplified by the examples.

Dated this 30TH day of **October, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1097 DEL 02

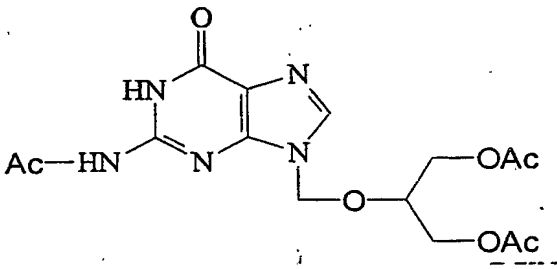
Ranbaxy Laboratories Limited

Application No.

No. of sheets = 05

Sheet 01 of 05

31 OCT 2002



FORMULA I

DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

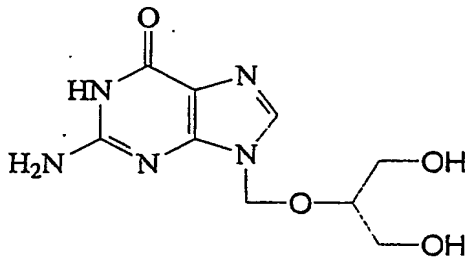
Application No.

No. of sheets = 05

Sheet 02 of 05

1007 DEL 02

31 OCT 2002

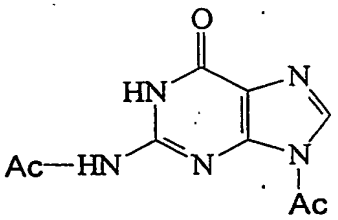


FORMULA II

DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary



FORMULA III

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

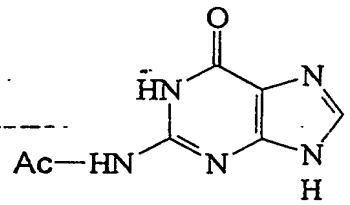
Application No.

No. of sheets = 05

Sheet 04 of 05

10 DEL 02

31 OCT 2002

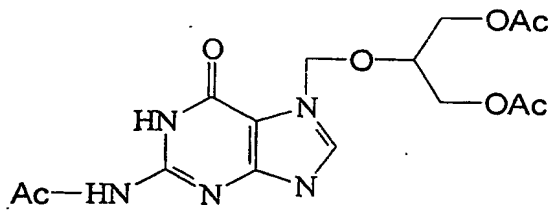


FORMULA IV

DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary



FORMULA V

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

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